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(54) **INHIBITEURS DU FACTEUR DE COAGULATION XA**

(54) **DIPEPTIDE INHIBITORS FOR THE BLOOD-CLOTTING FACTOR XA**

(57)

The invention relates to derivatives of amidino-benzylamine, especially derivatives of 4-amidino-benzylamine, with two bonded amino acids. These derivatives represent a novel group of highly active and very selective F Xa- inhibitors for treating cardiovascular diseases and thrombotic events.



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(54) Titre : INHIBITEURS DU FACTEUR DE COAGULATION XA

(54) Title: DIPEPTIDE INHIBITORS FOR THE BLOOD-CLOTTING FACTOR XA

(57) **Abrégé/Abstract:**

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(54) Title: DIPEPTIDE INHIBITORS FOR THE BLOOD-CLOTTING FACTOR XA

(54) Bezeichnung: DIPEPTIDISCHE HEMMSTOFFE FÜR DEN GERINNUNGSFAKTOR XA

(57) Abstract: The invention relates to derivatives of amidino-benzylamine, especially derivatives of 4-amidino-benzylamine, with two bonded amino acids. These derivatives represent a novel group of highly active and very selective F Xa-inhibitors for treating cardiovascular diseases and thrombotic events.

(57) Zusammenfassung: Die Erfindung betrifft Derivate des Amidino-Benzylamins, insbesondere solche des 4-Amidino-benzylamins, mit zwei gebundenen Aminosäuren, die eine neue Gruppe von hochaktiven und sehr selektiven F Xa-Hemmstoffen zur Behandlung kardiovaskulärer Erkrankungen und thrombotischer Ereignisse darstellen.

Inhibitors for the coagulation factor Xa

The invention relates to novel inhibitors for the
5 coagulation factor Xa for the treatment of
cardiovascular diseases and for the prevention of
thromboembolic events.

The anticoagulants of the heparin type or the vitamin K
10 antagonists presently employed clinically do not comply
with all requirements for an "ideal" antithrombotic.
Therefore alternatives are sought with low molecular
weight inhibitors of the coagulation enzymes,
especially of thrombin and factor Xa (F Xa). A
15 particular advantage of F Xa inhibitors in comparison
with thrombin inhibitors could be the lower tendency to
bleeding which has been shown in various animal
experiments. Thus the bleeding time was only minimally
influenced in antithrombotically effective doses (J. M.
20 Herbert et al., J. Pharmacol. Exp. Ther. 276, 1030-
1038, 1996; K. Sato et al., Brit. J. Pharmacol. 123,
92-96, 1998).

The first nonpeptide compounds having a high affinity
25 for F Xa were symmetrical bisbenzamidines ($K_i = 13$ nM
for the most active compound BABCH) (J. Stürzebecher et
al., Thromb. Res. 54, 245-252, 1998). The naphthamide
derivative DX-9065a has two basic groups and inhibits F
Xa selectively with $K_i = 24$ nM (T. Hara et al., Thromb.
30 Haemost. 71, 314-319, 1994). The inhibitor YM-60828 (K.
Sato et al., Eur. J. Pharmacol. 339, 141-146, 1997),
which is structurally related to DX-9065a, is even more
active ($K_i = 1.3$ nM). In the meantime, a whole series
of further bis-basic compounds have been described in
35 which, for example, two benzamide residues are linked
via an oxazoline ring ($K_i = 18$ nM) (M.L. Quan et al.,
Bioorg. Med. Chem. Lett. 7, 2813-2818, 1997) or a
carboxymethyl-alkyl chain ($K_i = 34$ nM) (T.P. Maduskuie

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et al., J. Med. Chem. 41, 53-62, 1998). The disadvantage of the bis-basic compounds is, in particular, the low bioavailability after oral administration.

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Inhibitors for F Xa which only contain one basic group have also been described. N-substituted amidinophenoxypyridines ($K_i = 0.11$ nM for BX-807834) were developed on the basis of BABCH (R. Mohan et al.,
10 Bioorg. Med. Chem. Lett. 8, 1877-1882, 1998; G.B. Phillips et al., J. Med. Chem. 41, 3557-3562, 1998). Amides of N α -adamantylloxycarbonyl-3-amidinophenylalanine ($K_i = 74$ nM for the most active compound) are selective inhibitors of F Xa (S. Sperl et al., Biol.
15 Chem. 381, 321-329, 2000), while N α -arylsulfonylaminoacylated esters of 3-amidinophenylalanine have a low inhibitory action ($K_i \approx 840$ nM for TAPAM) (J. Stürzebecher et al., Thromb. Res. 54, 245-252, 1998). WO 96/10022 discloses inhibitors which no longer have
20 any strong charge at all ($K_i = 3.0$ nM for the most active compound).

Until now, only a few peptides which are derived from the substrate sequence Ile-Glu-Gly-Arg have been
25 described as inhibitors of F Xa. The chloromethyl ketones described by Kettner and Shaw (Thromb. Res. 22, 645-652, 1981) inhibit F Xa irreversibly and are not suitable for in vivo applications. On the other hand, the peptides SEL 2489 ($K_i = 25$ nM) and SEL 2711 ($K_i =$
30 3 nM) are extremely active (J. A. Ostrem et al., Biochemistry 37, 1053-1059, 1998). Some peptidyl arginine aldehydes have also been described which, in addition to argininal in the P1 position, have a D-arginine or an unnatural basic amino acid in P3 (Z.H.
35 Jonathan, Bioorg. Med. Lett. 9, 3459-3464, 1999). However, so far no peptidyl agmatine derivatives are known as inhibitors of F Xa, although this type of inhibitor has led to considerable advances in the further development of thrombin inhibitors. In this

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case, the successes with compounds of the D-Phe-Pro-Arg type having a C-terminal agmatine and derivatives derived therefrom were particularly noteworthy. Picomolar K_i values were achieved for thrombin inhibition and the oral bioavailability was improved (T.J. Tucker et al., J. Med. Chem. 40, 1565-1569 and 3687-3693, 1997). In this case, however, no inhibition of F Xa was observed. For instance, melagatran, which has a 4-amidinobenzylamine residue at the C terminus and is very unspecific, inhibits F Xa with a $K_i = 2.8$ μ M. On the other hand, trypsin ($K_i = 4.0$ nM) and thrombin ($K_i = 2.0$ nM) are inhibited more than three orders of magnitude more strongly (D. Gustafsson et al., Blood Coagul. Fibrinolysis 7, 69-79, 1996).

The invention is based on the object of specifying an active compound which is also suitable for therapeutic applications and inhibits the coagulation factor Xa with high activity and specificity and which can be prepared with the lowest possible synthesis expenditure.

Surprisingly, it has been found that acylated amidinobenzylamine according to the general formula I shown in Patent claim 1, in particular compounds of 4-amidinobenzylamine in which X, R_1 , R_2 and R_3 result in natural and/or unnatural amino acids, inactivate factor Xa very efficaciously and selectively and effectively inhibit the coagulation of human blood plasma. Amidinobenzylamine in this case forms a particularly active inhibitor of factor Xa if the amidino group is in the 4-position, glycine and D-serine tert-butyl ether are bonded as amino acids and if the compound has an N-terminal protective group R_4 composed of an aryl- or aralkylsulfonyl residue.

Besides factor Xa, other enzymes were markedly less inhibited by the glycine derivatives, such that the derivatives of amidinobenzylamine according to the

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invention are a novel group of highly active and very selective F Xa inhibitors. In contrast to this, compounds which carry no H as R₁ (e.g. alanine derivatives) no longer selectively inhibit factor Xa, but are also strong inhibitors of trypsin, thrombin and plasmin.

The compounds are as a rule present as salts with mineral acids, preferably as hydrochlorides, or as salts with suitable organic acids.

The compounds of the general formula I can be prepared in a manner known in principle, as described below:

The starting compound 4-cyanobenzylamine is prepared from 4-cyanobenzyl bromide via Gabriel synthesis (G. Wagner and I. Wunderlich, Pharmazie 32, 76-77, 1977; B.C. Bookser and T.C. Bruice, J. Am. Chem. Soc. 113, 4208-4218, 1991). The Boc-protected acetyloxamidinobenzylamine is obtained from the 4-cyanobenzylamine thus prepared. The coupling of the further amino acids and of the protective group R₄ is carried out by means of standard coupling methods using Boc as an N-terminal protective group. The second amino acid can also be coupled directly as an N-aryl- or N-alkylsulfonyl-protected amino acid. The peptide analogs are synthesized sequentially, beginning from the acetyloxamidinobenzylamine. Most of the products crystallize well and can thus be simply purified. The purification of the inhibitors is carried out in the last stage by means of preparative, reversed-phase HPLC.

The invention will be illustrated in greater detail below with the aid of three working examples:

Working example 1:

Synthesis of benzylsulfonyl-D-Ser(Bz)-Gly-4-amidino-
benzylamide x HCl

5

1.1 Boc-4-cyanobenzylamide

20 g (0.151 mol) of 4-cyanobenzylamine were dissolved
in 300 ml of H₂O, 150 ml of dioxane and 150 ml of 1 N
10 NaOH. 37.5 ml of di-tert-butyl dicarbonate were added
dropwise with ice cooling and the mixture was stirred
at 0°C for one hour and at room temperature for a
further 24 hrs. The dioxane was removed i.v. and the
aqueous residue was extracted 3 times with ethyl
15 acetate. The combined extracts were washed 3 times with
5% strength KHSO₄ solution and 3 times with saturated
NaCl solution, dried over Na₂SO₄ and concentrated i.v.
(white crystals). HPLC: acetonitrile/H₂O, elution in
44.1% acetonitrile; yield: 30.48 g (0.131 mol), 87%.

20

1.2 Boc-4-acetyloxamidinobenzylamide

According to Judkins et al. (Synthetic Comm. 26, 4351-
4367, 1996), 30.48 g (0.131 mol) of Boc-4-
25 cyanobenzylamide were dissolved in 300 ml of abs.
ethanol with 13.65 g (0.197 mol) of hydroxylamine x HCl
and 34 ml (0.197 mol) of DIEA. The solution was
refluxed for 2 hrs and stirred at room temperature
overnight. The batch was then concentrated i.v., the
30 residue was dissolved in about 200 ml of acetic acid
and the solution was treated with 18.67 ml (0.197 mol)
of acetic anhydride. After 1 hr, it was again
concentrated, dissolved in ethyl acetate and washed 3
times each with 5% strength KHSO₄ solution and
35 saturated NaCl solution at 0°C. After drying over Na₂SO₄
and concentrating i.v., a white powder precipitated.
HPLC: acetonitrile/H₂O, elution in 32.0% acetonitrile;
yield: 31.3 g (0.102 mol) 78%.

1.3 4-Acetyloxamidinobenzylamine x HCl

5 mmol of Boc-4-acetyloxamidinobenzylamide are dissolved in 20 ml of 1 N HCl in glacial acetic acid and the solution is allowed to stand at room temperature for 45 min. It is then largely concentrated i.v., and the product is precipitated using dry diethyl ether, filtered off on a frit, washed again with fresh ether and dried i.v. On account of the quantitative reaction, the product was employed for the next synthesis step without further purification.

1.4 Boc-Gly-4-acetyloxamidinobenzylamide

The coupling of Boc-Gly-OH (Orpegen, Heidelberg) to 4-acetyloxamidinobenzylamine was carried out according to Frérot et al. (Tetrahedron 47, 259 ff., 1991). To this end, 2.064 g (9.3 mmol) of 4-acetyloxamidinobenzylamine x HCl and 1.629 g (9.3 mmol) of Boc-Gly-OH were dissolved in about 25 ml of DMF. 4.84 g (9.3 mmol) of PyBOP and 3.878 ml (27.9 mmol) of TEA were then added at 0°C and the pH was adjusted to 9 using TEA. After stirring at room temperature for 1 hr, the mixture was concentrated i.v., taken up in ethyl acetate and subjected to acidic, basic and neutral washing 3 times each, dried and concentrated. Yield: 3 g (8.2 mmol) 88%.

1.5 Boc-Gly-4-amidinobenzylamide x AcOH

3 g (8.2 mmol) of Boc-Gly-4-acetyloxamidinobenzylamide were dissolved in 200 ml of 90% strength acetic acid. 300 mg of 10% palladium on activated carbon were then added under argon. Argon was replaced by a hydrogen atmosphere and the batch was hydrogenated for 24 hrs with vigorous stirring. The catalyst was filtered off and the filtrate was concentrated i.v.. Yield: 2.9 g (7.9 mmol) 96%.

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1.6 H-Gly-4-amidinobenzylamide x 2 HCl

2.9 g (7.9 mmol) of Boc-Gly-4-amidinobenzylamide were dissolved in 100 ml of 1 N HCl in glacial acetic acid and the solution was allowed to stand at room temperature for 45 min. It was then largely concentrated i.v. and precipitated using dry diethyl ether, then filtered off on a frit and the product was again washed with fresh ether. After drying the product i.v., it was used without further purification for the synthesis according to item 1.8.

1.7 Benzylsulfonyl-D-Ser(Bz)-OH

229 mg (1.173 mmol) of H-D-Ser(Bz)-OH and 408 μ l (2.345 mmol) of DIEA were dissolved in 50 ml of 50% acetonitrile. 335 mg (1.76 mmol) of benzylsulfonyl chloride were then added and the mixture was stirred at room temperature for 12 hrs. It was concentrated i.v., taken up using ethyl acetate and subjected to acidic and neutral washing 3 times each. After drying over sodium sulfate, it was concentrated i.v. Yield: 289 mg (0.827 mmol) 71%.

1.8 Benzylsulfonyl-D-Ser(Bz)-Gly-4-amidinobenzylamide x TFA

151 mg (0.433 mmol) of benzylsulfonyl-D-Ser(Bz)-OH and 121 mg (0.433 mmol) of H-Gly-4-amidinobenzylamide x 2 HCl were dissolved in a little abs. DMF. 225 mg (0.433 mmol) of PyBOP and 230 μ l (1.32 mmol) of DIEA were added with ice cooling. After stirring at room temperature for 1 hr, the mixture was concentrated i.v. and the product was purified by means of HPLC (acetonitrile/H₂O, 0.1% trifluoroacetic acid, elution in 37.4% acetonitrile). Yield: 232 mg (0.356 mmol) 82%.

Working example 2:

Inhibition of F Xa by selected compounds having Y = amidino

5

R ₄	R ₃ configuration	R ₃	R ₂	X-R ₁	Amidino position	K _b μM
H	L	CH ₂ -OH	H	CH ₂	4	> 1000
Boc	L	CH ₂ -OH	H	CH ₂	4	110
H	D	CH ₂ -OH	H	CH ₂	4	> 1000
Ac	D	CH ₂ -OH	H	CH ₂	4	> 1000
Bz-SO ₂	D	CH ₂ -OH	H	CH ₂	4	3.0
Bz-SO ₂	D	CH ₂ -O-Bz	H	CH ₂	4	0.050
Bz-SO ₂	D	CH ₂ -O-tBu	H	CH ₂	4	0.030
Bz-SO ₂	D	CH ₂ -O-tBu	H	CH ₂ -CH ₃	4	0.044
H	D	CH ₂ -O-Bz	H	CH ₂	3	140
Boc	D	CH ₂ -O-Bz	H	CH ₂	3	93
Bz-SO ₂	D	CH ₂ -O-Bz	H	CH ₂	3	84

Determination of the inhibitory action

For the determination of the inhibitory action, 200 μl of tris buffer (0.05 M, 0.154 M NaCl, 5% ethanol, pH 8.0; contains the inhibitor), 25 μl of substrate (Moc-D-Nle-Gly-Arg-pNA in H₂O; Pentapharm Ltd., Basle, Switzerland) and 50 μl of F Xa (from Rind, Diagnostic Reagents Ltd, Thame, GB) were incubated at 25°C. After 3 min, the reaction was interrupted by addition of 25 μl of acetic acid (50%) and the absorption at 405 nm was determined by means of microplate reader (MR 5000, Dynatech, Denkendorf, Germany). The K_i values were

determined according to Dixon (Biochem. J. 55, 170-171, 1953) by linear regression by means of a computer program. The K_i values are the mean of at least three determinations.

5

Working example 3:

Inhibition of the coagulation of human plasma by
benzylsulfonyl-D-Ser(Bz)-Gly-4-amidinobenzylamide

10

Concentration μM	Prolongation of the <u>coagulation</u> time (%)	
	aPTT	PT
3.3	385	386
1.7	260	266
0.83	185	198
0.42	146	153
0.21	122	127
0.1	111	119

Determination of the inhibition of coagulation

- 15 For the determination of the prothrombin time (PT),
100 μl of thromboplastin (Dade, Unterschleißheim) and
100 μl of inhibitor, dissolved in CaCl_2 (0.05 M, 5%
ethanol) were incubated at 37°C for 2 min and the
coagulation was started by addition of 100 μl of human
20 citrate plasma. For the determination of the activated
partial thromboplastin time (aPTT), 100 μl of human
citrate plasma were incubated with 100 μl of aPTT
reagent (Roche Diagnostics, Mannheim) at 37°C for 3 min
and the coagulation was started by addition of 100 μl
25 of inhibitor, dissolved in CaCl_2 (0.05 M, 5% ethanol).
The coagulation times were determined using the
Thrombotrack coagulometer (Immuno, Heidelberg).

Abbreviations used:

	Ac	acetyl
	Boc	tert-butyloxycarbonyl
5	Bz	benzyl
	DIEA	diisopropylethylamine
	DMF	N,N-dimethylformamide
	i.v.	in vacuo
10	PyBOP	benzotriazol-1-yl-N-oxytris- (pyrrolidino)phosphonium hexafluorophosphate
	TEA	triethylamine
15	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	tBu	tert-butyl

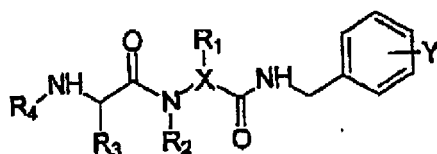
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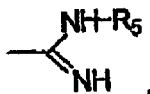
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Patent claims

1. Inhibitors for the coagulation factor Xa of the
 5 general formula I:



- in which the substituent Y occurs in the 3- or 4-
 10 position and is an amidino group



- in which R₅ has an H, an OH or a carbonyl residue -CO-R
 15 or oxycarbonyl residue -COO-R, where R can be a
 branched or unbranched alkyl having 1-16 C atoms, a
 substituted or unsubstituted aryl or heteroaryl residue
 or a substituted or unsubstituted aralkyl or
 heteroaralkyl residue,

20

X is a CH group or N,

- R₁ is H or a branched or unbranched alkyl having 1-8 C
 atoms or (CH₂)_n-OH where n = 1-5,

25

R₂ is an H or a branched or unbranched alkyl having 1-8
 C atoms,

- R₃ is a branched or unbranched alkyl having 1-8 C atoms
 30 or a (CH₂)_n-O-R₆, (CH₂)_n-S-R₆ or (CH₂)_n-NH-R₆ where n = 1-
 5 and R₆ is a branched or unbranched alkyl having 1-16
 C atoms, a substituted or unsubstituted aryl or
 heteroaryl residue or a substituted or an unsubstituted
 aralkyl or heteroaralkyl residue and

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R₄ is a sulfonyl residue -SO₂-R, a carbonyl residue -CO-R, an oxycarbonyl residue -COO-R or an H, where R is a branched or unbranched alkyl having 1-16 C atoms, a substituted or an unsubstituted aryl or heteroaryl residue, a substituted or unsubstituted aralkyl or heteroaralkyl residue, an adamantyl residue, a camphor residue or a cyclohexylmethyl residue.

2. Inhibitors according to Claim 1, characterized in that, in the amidinobenzylamide, the amidino group is in the 4-position and that the amino acids Gly and D-Ser(tBu) and, as R₄, an aryl or an aralkylsulfonyl residue are bonded thereto.

3. Use of the inhibitors according to Claim 1 for the preparation of orally, subcutaneously, intravenously or transdermally administrable medicaments for the prevention or treatment of thromboembolic diseases.

4. Use according to Claim 3, characterized in that the inhibitors are employed as medicaments in the form of tablets, coated tablets, capsules, pellets, suppositories, solutions or patches, etc.

5. Use of the inhibitors according to Claim 1 as a diagnostic agent, in particular in thrombotic events.